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(54) Title: SHIP 1 MODULATORS

(57) Abstract: The present invention includes the use of pelorol and related sesquiterpene compounds as modulators of SHIP 1 activity. This invention also provides novel sesquiterpene compounds capable of modulating SHIP 1 activity and methods of synthesis thereof.

SHIP 1 MODULATORS

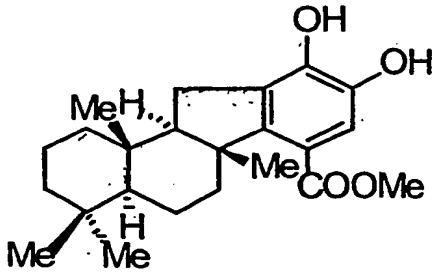
Technical Field of the Invention

The present invention relates to SHIP 1, a regulator of cell proliferation and survival and immune cell activity.

Background of the Invention

SH_2-containing inositol 5-phosphatase (SHIP 1), is an important negative regulator of cell proliferation and survival, as well as of immune cell activation. United States Patent No. 6,238,903 discloses that SHIP 1 is an enzyme regulator of signaling pathways that control gene expression, cell proliferation, differentiation, activation, and metabolism, particularly of the Ras and phospholipid signaling pathways. SHIP 1 disrupted (SHIP 1 -/-) mice exhibit a myeloproliferative phenotype characterized by overproduction of granulocytes and macrophages[1]. SHIP 1 -/- mast cells are more prone to IgE and Steel factor induced degranulation, while SHIP 1 -/- B cells are resistant to negative regulation by Fc RIIB. SHIP 1 is also involved in the pathogenesis of chronic myelogenous leukemia[2].

A sesquiterpene compound termed pelorol may be obtained from various marine sponge species, including *Petrosaspongia metachromia* and *Dactylospongia elegans*. Kwak et al. and Goelik et al. each disclosed the structure of pelorol and its extraction from different marine sponges.[3,4] The precise structure of pelorol is shown below, with Me representing a methyl group.

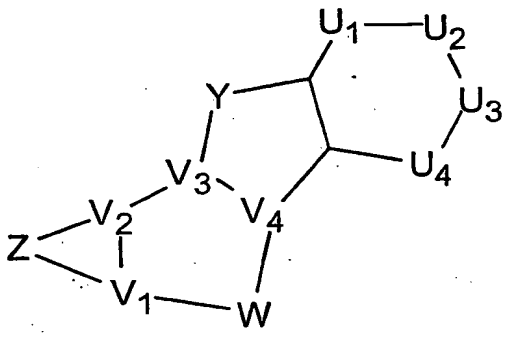


Summary of the Invention

This invention is based on the discovery that pelorol and related compounds are capable of modulation of SHIP 1 activity.

This invention provides a compound or a pharmaceutically acceptable salt thereof, the compound being capable of modulation of SHIP 1 activity,

wherein the compound does not have the precise structure of pelorol but is a compound of Formula I:



I

wherein:

the ring comprising U_1-U_4 is aromatic and U1, U_2, U_3, and U_4 are independently selected from the group consisting of: CH, N, NH, NR, C=O, CX, and CR_1;

V_1, V_2, V_3, and V_4 are independently selected from the group consisting of: CH, CR_1, CX, and C=;

Z is a saturated, partially unsaturated, or unsaturated linear alkyl chain of between one and six carbons that may be substituted with one or more of: R_1, epoxide, ketone (=O), thiocarbonyl (=S), oxime (=N-OH), -OH, -OR, -O_2CR, -SH, -SR, -SOCR, -NH_2, -NHR, -NR_2, -NR_3^+, -NHCOR, -I, -Br, -Cl, -F, -CN, -CO_2H, -CO_2R, -CHO, -COR, -$CONH_2$, -CONHR, NRCOR, -$CONR_2$, -COSR -NO_2, -OSO_3H, -SO_3H , -SOR, or -SO_2R; wherein one or more CH_2 groups in the alkyl chain may be replaced by O, S, or NR; and one or more C or CH groups in the alkyl chain may be replaced with NR;

W is a saturated, partially unsaturated, or unsaturated linear alkyl chain of between one and six carbons that may be substituted with one or more of: R_1, epoxide, ketone (=O), thiocarbonyl (=S), oxime (=N-OH), -OH, -OR, -O_2CR, -SH, -SR, -SOCR, -NH_2, -NHR, -NR_2, -NR_3^+, -NHCOR, -I, -Br, -Cl, -F, -CN, -CO_2H, -CO_2R, -CHO,

-COR, -$CONH_2$, -CONHR, NRCOR, -$CONR_2$, -COSR -NO_2, -OSO_3H, -SO_3H , -SOR, or -SO_2R; and one or more CH_2 groups in the alkyl chain may be replaced by O, S, or NR; and one or more C or CH groups in the alkyl chain may be replaced with NR;

Y is a saturated, partially unsaturated, or unsaturated linear alkyl chain of between one and six carbons that may be substituted with one or more of: R_1, epoxide, ketone (=O), thiocarbonyl (=S), oxime (=N-OH), -OH, -OR, -O_2CR, -SH, -SR, -SOCR, -NH_2, -NHR, -NR_2, -NR_3^+, -NHCOR, -I, -Br, -Cl, -F, -CN, -CO_2H, -CO_2R, -CHO, -COR, -$CONH_2$, -CONHR, NRCOR, -$CONR_2$, -COSR -NO_2, -OSO_3H, -SO_3H , -SOR, or -SO_2R; and one or more CH_2 groups in the alkyl chain may be replaced by O, S, or NR; and one or more C or CH groups in the alkyl chain may be replaced with NR;

R_1 is selected from the group consisting of: methyl; and a linear, branched, or cyclic saturated, partially saturated, or unsaturated alkyl group containing one to ten carbons that may be substituted with one or more of: -OH, -OR, =O, =S, =N-OH, -O_2CR, -SH, -SR, -SOCR, -NH_2, -NHR, -NR_2, -NR_3^+, -NHCOR, -I, -Br, -Cl, -F, -CN, -CO_2H, -CO_2R, -CHO, -COR, -$CONH_2$, -CONHR, NRCOR, -$CONR_2$, -COSH, -COSR-, CSOR, NO_2, -OSO_3H, -SO_3H, , -SOR, or -SO_2R;

X is selected from the group consisting of: OH, -OR, -O_2CR, -SH, -SR, -SOCR, -NH_2, -NHR, -NR_2, -NR_3^+, -NHCOR, -I, -Br, -Cl, -F, -CN, -CO_2H, -CO_2R, -CHO, -COR, -$CONH_2$, -CONHR, NRCOR, -$CONR_2$, -COSH, -COSR-, CSOR, NO_2, -OSO_3H, -SO_3H, , -SOR, -SO_2R, -SO_2NH_2, -SO_2NHR, and -SO_2NR_2; and,

R is a linear, branched, or cyclic one to ten carbon, saturated, partially saturated, or unsaturated alkyl group. The aromatic ring comprising U_1-U_4 includes ortho and para-quinones.

The following are preferred components and substituents for Formula I, which may be independently selected and in any combination. Preferably, U_1, U_2, U_3 and U_4 are independently CH, CX, or CR_1; Z is an alkyl chain of 3, 4, or 5 atoms, more preferably being carbon atoms or carbons in C, CH, or CH_2 groups which have been replaced as defined; W is an alkyl chain of 2 or 3 atoms, more preferably being carbon atoms or carbons in C, CH or CH_2 groups which have been replaced as defined; and/or Y is an alkyl chain of between 1 and 3 atoms, more preferably being carbon atoms or carbons in C, CH, or CH_2 groups which have been replaced as defined. Even more preferably, Z has

a chain of 4 atoms as defined; W has a chain of 2 atoms as defined; and/or Y has a chain of 1 or 2 atoms as defined. It is also even more preferred that the atoms of the chains of Z, W, and Y and the ring comprising U_1-U_4 be carbon atoms.

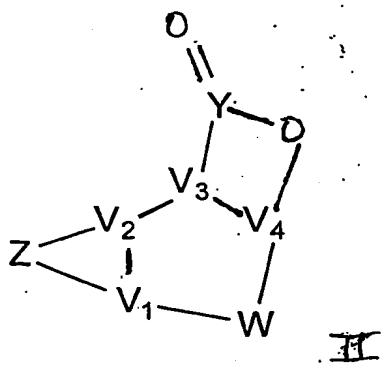
This invention also provides a pharmaceutical composition for the treatment or prevention of an immune, inflammatory, or neoplastic condition or disorder comprising pelorol or another compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. Such compositions may comprise two or more different compounds of Formula I, one of which may be pelorol.

This invention also provides a method of treatment or prevention of an immune, inflammatory, or neoplastic disorder or condition, comprising administering to a patient in need of such treatment or prevention, an effective amount of pelorol or other compound of Formula I, or a pharmaceutically acceptable salt thereof.

This invention also provides the use of pelorol or another compound of Formula I, or a pharmaceutically acceptable salt thereof, for modulation of SHIP 1 activity and for preparation of agents for the modulation of SHIP 1 activity. Such modulation may be *in vitro* or *in vivo*. Agents for *in vivo* use include the pharmaceutical composition described above and the modulation may be for the above described treatment or prevention of conditions or disorders.

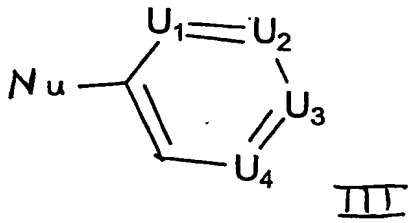
Compounds of Formula I including pelorol may be prepared in whole or in part from natural sources such as by fractionating extracts of marine sponges, or synthesized according to methods as disclosed herein.

This invention also provides a method of making a compound of Formula I, comprising: combining a lactone of Formula II:



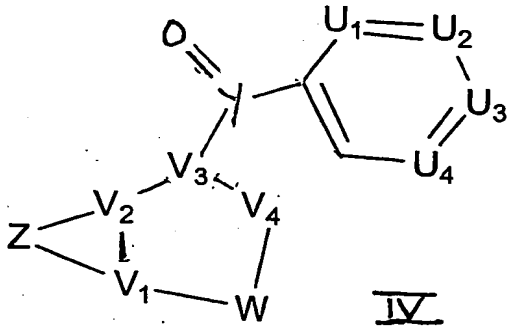
II

in which V_1-V_4, Y, W and Z are as defined for Formula I, with an aromatic ring of Formula III:



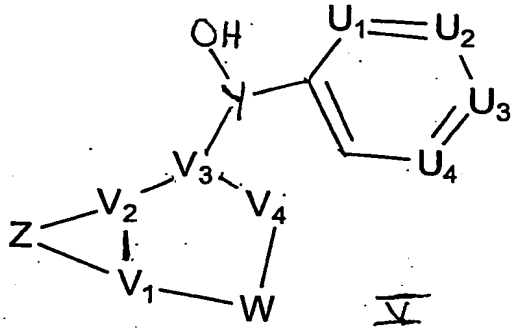
III

in which U_1-U_4 are as defined for Formula I and Nu is a nucleophilic reactive group, to produce a compound of Formula IV:



IV

reducing the compound of Formula IV to produce a compound of Formula V:



V

condensing the compound of Formula V to produce a compound of Formula I.

Component Y in compounds of Formula I produced by the preceding method from a single compound of Formula II may have different degrees of saturation as compared to Y in the starting material (see Tables 1 and 2 for examples). In order to reduce the number of atoms in the ring of Formula I which comprises Y (e.g. from a 6 membered ring to a 5 membered ring), a compound of Formula I having an unsaturated Y

may be selected and subjected to oxidizing and reduction steps to reduce the size of the ring comprising Y.

A preferred embodiment of the preceding method starts with an aromatic compound of Formula I comprising a (non-heterocyclic) ring of carbon atoms. A preferred nucleophile (Nu) is lithium (Li) which may be substituted onto the ring for a halogen such as bromine (Br) at the same time as combination of the aromatic starting material with a compound of Formula II. Preferably, U_1-U_4 are CX or CR_1, with R_1 preferably being limited to R as defined above. Preferably, U_2 in the starting material of Formula III is an activating group such as -OMe or NHAc (Me = methyl and Ac = acyl) which group may be subsequently converted to a desired substituent for U_2. Substitutents may also be protected, where appropriate with a protecting group (P) such as TBS.

Pelorol and other compounds having the structure of Formula I exhibit SHIP 1 agonist activity. By activating SHIP 1, such agonists are particularly useful in the treatment of inflammatory diseases, such as those involving macrophage proliferation or activation, neoplastic diseases such as myeloid and lymphoid leukemias, as an immunosuppressive agent and for affecting mast cell degeneration such as in the treatment or prevention of allergies.

Brief Description of the Drawings

The figures of the invention are best understood when read in conjunction with the following detailed description and the examples.

Figure 1 is a graph depicting the effect of sponge extracts on SHIP 1 activity *in vitro*. The assay was performed in 96-well microtitre plates. SHIP 1 enzyme was produced with a hemagglutinin and a hexahistidine tag, from a mammalian expression vector. The His tag was employed to enhance purification. SHIP 1 enzyme (10ng) was incubated with extract or DMSO for 15 minutes at room temperature before addition of 200 M inositol-1,3,4,5-tetrakisphosphate. The reaction was allowed to proceed for 20 minutes at 37 degrees C. The amount of inorganic phosphate released was then assessed by the addition of malachite green reagent followed by an absorbance measurement at 650 nm.

Figure 2 is a graph depicting the effect of pelorol on macrophage nitric oxide (NO) production. Wild-type or SHIP 1 -/- macrophage cells were aliquoted into

microtitre plates ($5x10^4$/well) and activated with 1 g/mL endotoxin in the presence or absence of PNG95-127 or DMSO carrier. The cells were incubated at 37 degrees C, 5% CO_2 for 24 hours and the culture supernatant was removed for NO determination using the Griess reagent, as shown.

Detailed Description of the Invention

In a preliminary screen of 150 marine organism extracts, two extracts which activated SHIP 1 were identified (Figure 1). SHIP 1 assay-guided fractionation of one of these extracts resulted in the identification of the active compound as being pelorol. The origin and processing of the extracts which tested positive in the screen is described in the paragraph immediately below.

Specimens of the brownish sheet sponge *Dactylospongia elegans* (order Dictyoceratida, family Spongiidae) were collected by hand using SCUBA at a depth of 5-10 m from a protected overhang in Rasch Passage on the outer reef of Madang Lagoon, Papua New Guinea, in January 1995. Freshly collected sponge was frozen on sight and transported to Vancouver, Canada over dry ice. The sponge was identified and for verification, a voucher sample was placed in the Zoological Museum of Amsterdam (ZMA POR. 15986). The frozen sponge (120 g) was cut into small pieces, immersed in and subsequently extracted repeatedly with MeOH (3 x 250 mL). The combined methanolic extracts were concentrated *in vacuo* and then partitioned between EtOAc (4 x 100 mL) and H_2O (300 mL). The combined EtOAc extract was evaporated to dryness *in vacuo* to yield 490 mg of a brownish purple oil, found to contain pelorol.

A synthetic scheme for making pelorol and other compounds of Formula I is set out above. The following Tables (1-5) provide detailed examples of such synthesis and examples of different compounds of Formula I prepared thereby. In the following Tables, the ring comprising component Y as defined in Formula I is termed the "C" ring. An analog identical to pelorol except that the "C" ring has six members, is termed "homopelorol".

TABLE 1: Example of synthesis of compounds of Formula I where the aromatic ring comprising U_1-U_4 is a benzene ring. Here, substituents are as defined for Formula I with R being R_1 as in Formula I, limited to methyl and unsubstituted alkyl groups. X_1-X_3 is X or R_1 as defined in formula I or is H. Preferably, X_2 is an activating group such as OMe and NHAc. ArBr is a halogen (Br) substituted benzene ring for which replacement of the halogen provides a compound of Formula III in which Nu is Li.

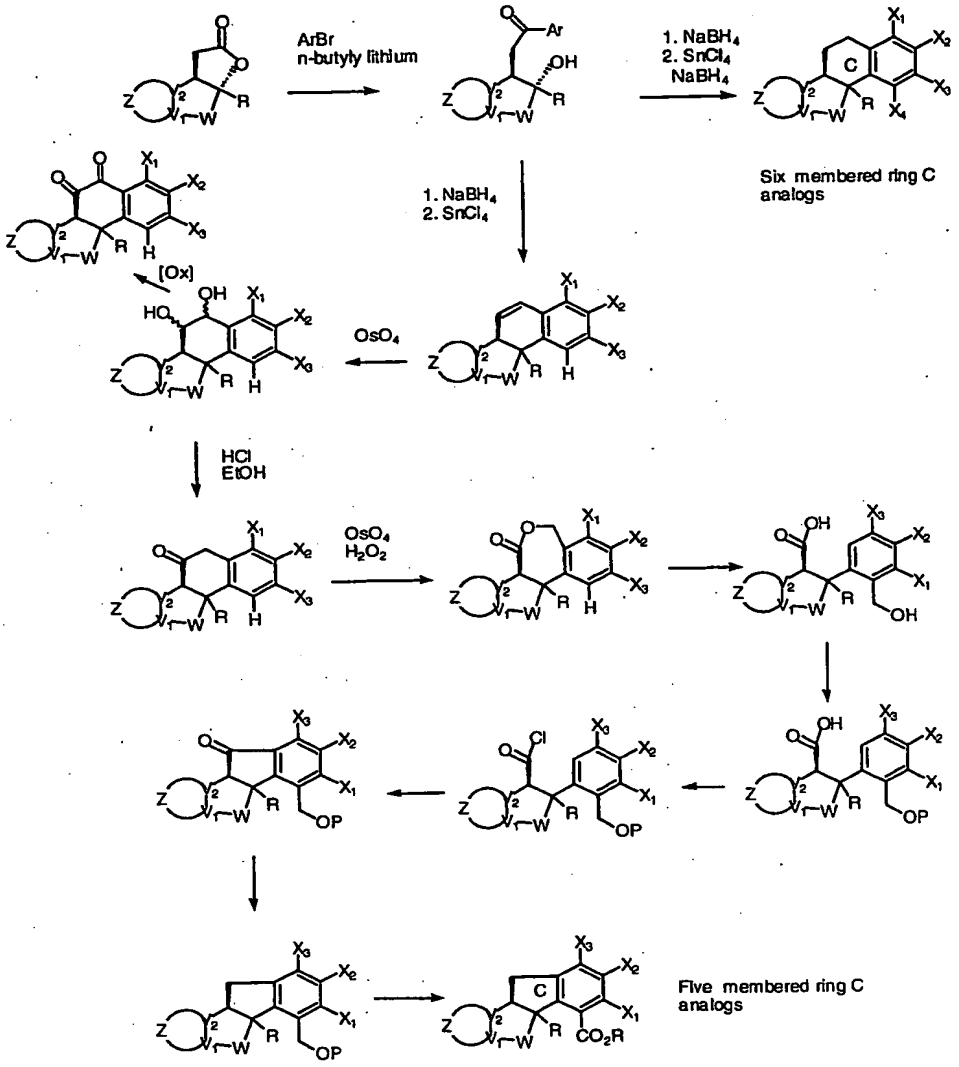


TABLE 2: Example of synthesis of pelorol and 5 and 6 membered ring analogs starting with sclareolide as the compound of Formula II. Terminology and preferences are as described for Table I.

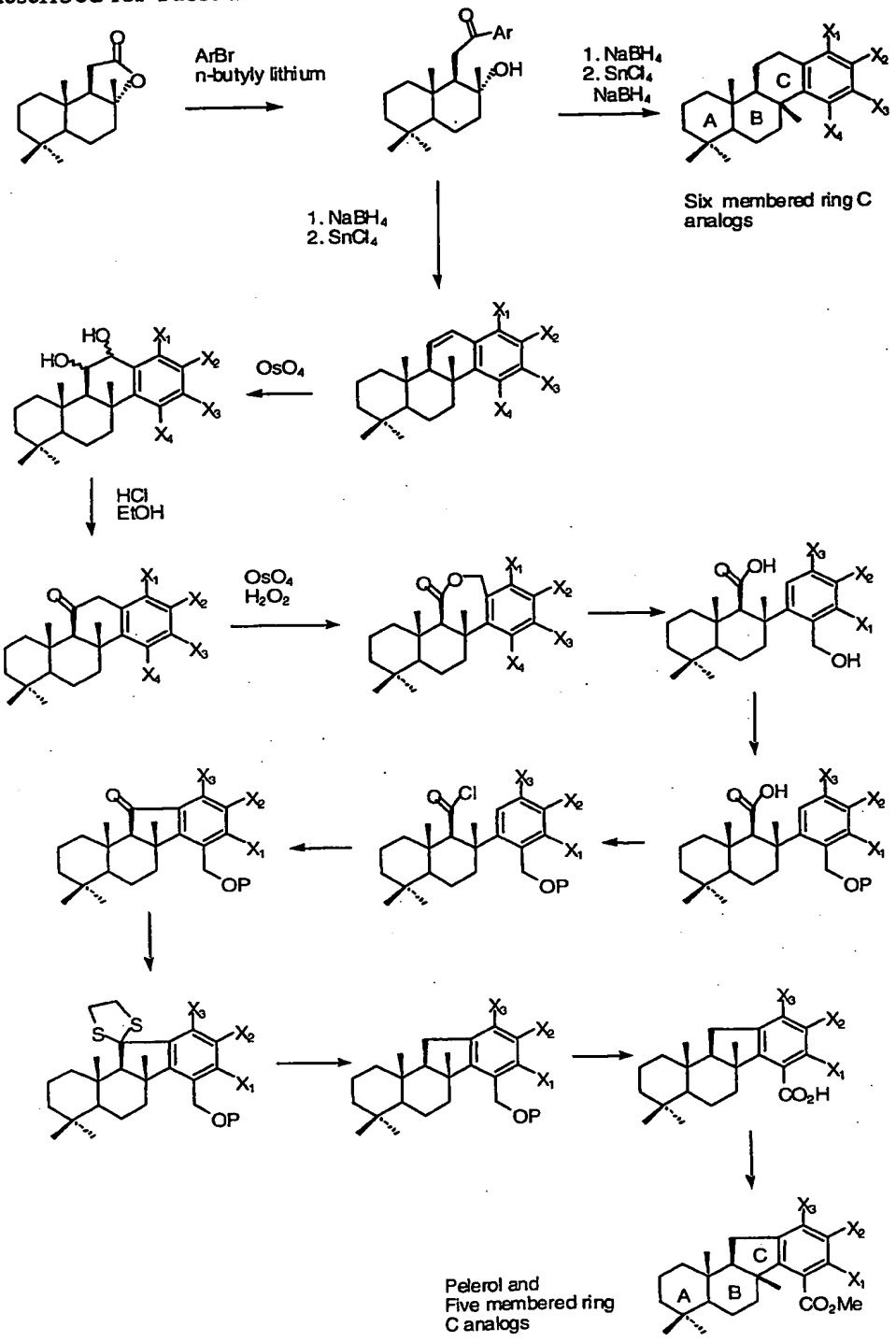


TABLE 3: Example of synthesis of homopelorol.

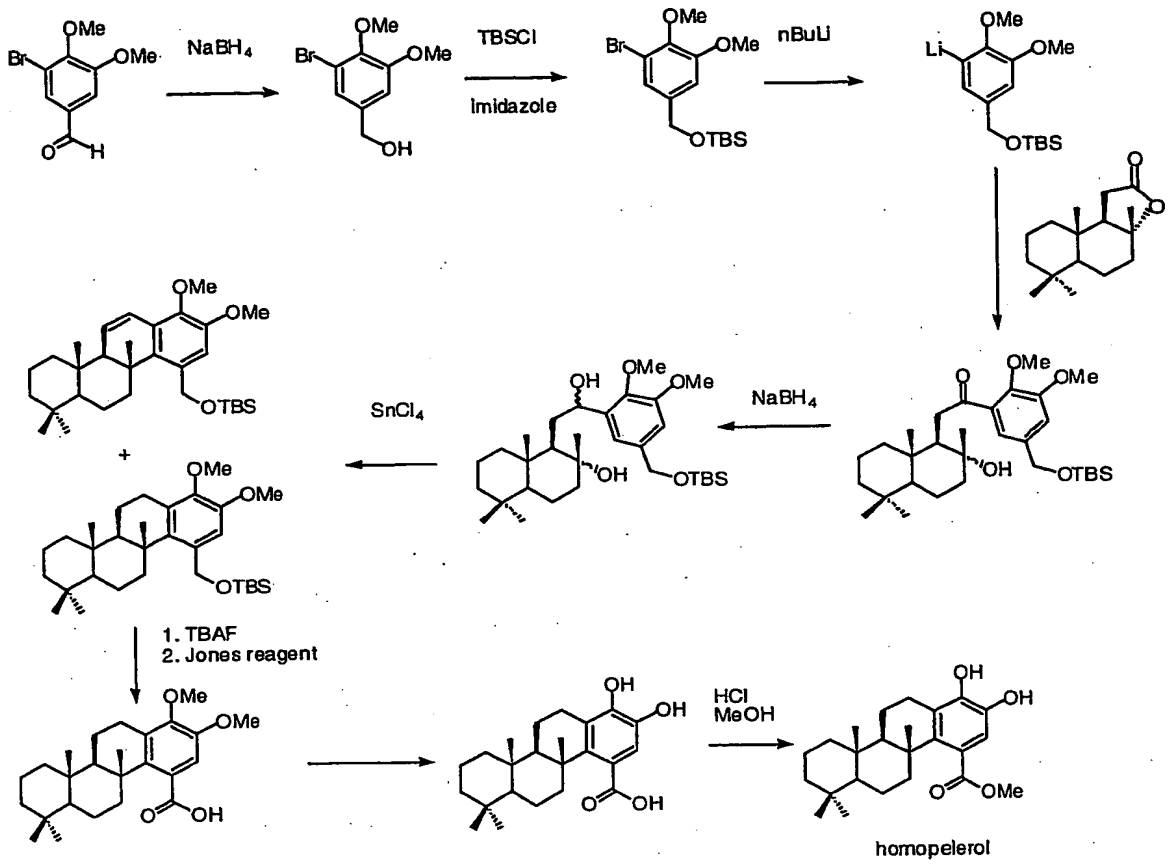


TABLE 4: Example of synthesis of PNSR-4A, a homopelorol analog.

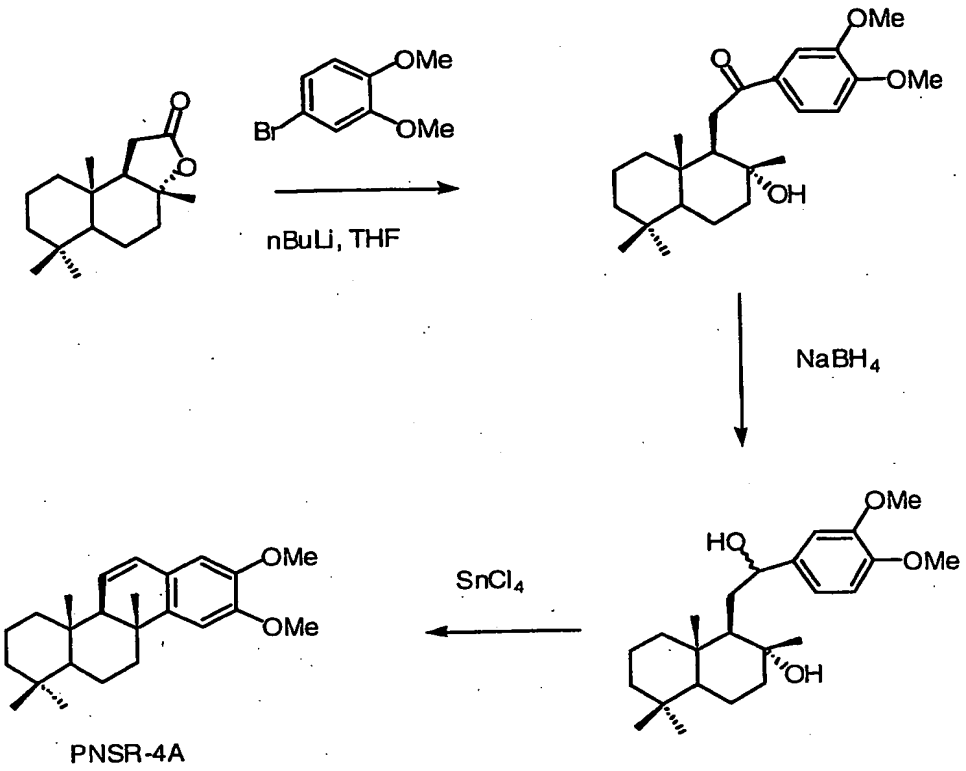
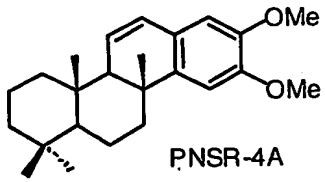
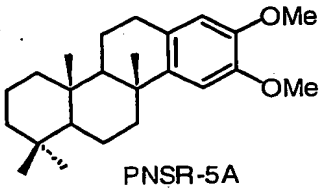


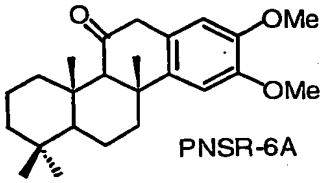
TABLE 5: Example 5 of homopelorol analogs made by preceding methods.



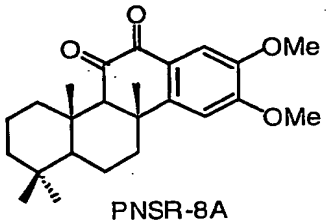
PNSR-4A



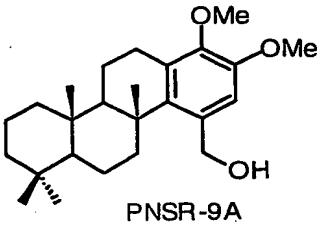
PNSR-5A



PNSR-6A



PNSR-8A



PNSR-9A

Pelorol and SHIP 1 agonist compounds of this invention exhibit anti-inflammatory actions on macrophages and mast cells in intact cell-based assays, and inhibit nitric oxide production from endotoxin activated wild-type macrophages. Results obtained for pelorol are shown in Figure 2. Such inhibition is not observed in SHIP 1 -/- macrophages. Pelorol and compounds of this invention also inhibit IgE induced mast cell degranulation.

Compounds for use in this invention may be formulated into pharmaceutical compositions in any number of ways, which would be known to a person of skill in the art, all of which are within the scope of the invention. The person of skill in the art may be expected to select appropriate pharmaceutically acceptable salts as well as appropriate pharmaceutically acceptable excipients, diluents, and carriers.

SHIP 1 modulators and pharmaceutical compositions of this invention may be administered to patients in need of treatment for cancer (neoplastic diseases), other cell proliferative disorders, inflammatory diseases and immune diseases. Treatment of neoplastic diseases such as, but not limited to, leukemias, carcinomas, sarcoma, melanomas, neuroblastoma, capillary leak syndrome and hematological malignancies are within the scope of this invention. Diseases with an inflammatory component include, but are not limited to, rheumatoid arthritis, multiple sclerosis, Guillan-Barre syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease, host versus graft, lupus erythematosis, Alzheimer's disease and insulin-dependent diabetes mellitus. Diseases related to inappropriate activation of macrophage-related cells of the reticuloendothelial lineage include osteoporosis.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of skill in the art in light of the teachings of this invention that changes and modification may be made thereto without departing from the spirit or scope of the appended claims. All patents, patent applications and publications referred to herein are hereby incorporated by reference.

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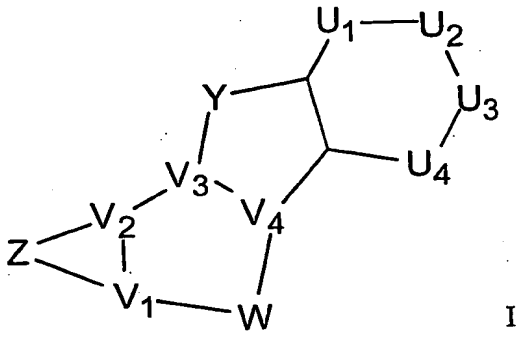
We claim:

1. A compound capable of modulation of SHIP 1 activity, the compound being of Formula I or a pharmaceutically acceptable salt thereof,



I

wherein:

the ring comprising U_1-U_4 is aromatic and U_1, U_2, U_3, and U_4 are independently selected from the group consisting of: CH, N, NH, NR, C=O, CX, and CR_1;

V_1, V_2, V_3, and V_4 are independently selected from the group consisting of: CH, CR_1, CX, and C=;

Z is a saturated, partially unsaturated, or unsaturated linear alkyl chain of between one and six carbons that may be substituted with one or more of: R_1, epoxide, =O, =S, =N-OH, -OH, -OR, -O_2CR, -SH, -SR, -SOCR, -NH_2, -NHR, -NR_2, -NR_3^+, -NHCOR, -I, -Br, -Cl, -F, -CN, -CO_2H, -CO_2R, -CHO, -COR, -$CONH_2$, -CONHR, NRCOR, -$CONR_2$, -COSR -NO_2, -OSO_3H, -SO_3H , -SOR, or -SO_2R; wherein one or more CH_2 groups in the alkyl chain may be replaced by O, S, or NR; and one or more C or CH groups in the alkyl chain may be replaced with NR;

W is a saturated, partially unsaturated, or unsaturated linear alkyl chain of between one and six carbons that may be substituted with one or more of: R_1, epoxide, =O, =S, =N-OH, -OH, -OR, -O_2CR, -SH, -SR, -SOCR, -NH_2, -NHR, -NR_2, -NR_3^+, -NHCOR, -I, -Br, -Cl, -F, -CN, -CO_2H, -CO_2R, -CHO, -COR, -$CONH_2$, -CONHR, NRCOR, -$CONR_2$, -COSR -NO_2, -OSO_3H, -SO_3H , -SOR, or -SO_2R; and one or more CH_2 groups in the alkyl chain may be replaced by O, S, or NR; and one or more C or CH groups in the alkyl chain may be replaced with NR;

Y is a saturated, partially unsaturated, or unsaturated linear alkyl chain of between one and six carbons that may be substituted with one or more of: R_1, epoxide, =O, =S, =N-OH, -OH, -OR, $-O_2CR$, -SH, -SR, -SOCR, $-NH_2$, -NHR, $-NR_2$, $-NR_3^+$, -NHCOR, -I, -Br, -Cl, -F, -CN, $-CO_2H$, $-CO_2R$, -CHO, -COR, $-CONH_2$, -CONHR, NRCOR, $-CONR_2$, -COSR $-NO_2$, $-OSO_3H$, $-SO_3H$, -SOR, or $-SO_2R$; and one or more CH_2 groups in the alkyl chain may be replaced by O, S, or NR; and one or more C or CH groups in the alkyl chain may be replaced with NR;

R_1 is selected from the group consisting of: methyl; and a linear, branched, or cyclic saturated, partially saturated, or unsaturated alkyl group containing one to ten carbons that may be substituted with one or more of: -OH, -OR, =O, =S, =N-OH, $-O_2CR$, -SH, -SR, -SOCR, $-NH_2$, -NHR, $-NR_2$, $-NR_3^+$, -NHCOR, -I, -Br, -Cl, -F, -CN, $-CO_2H$, $-CO_2R$, -CHO, -COR, $-CONH_2$, -CONHR, NRCOR, $-CONR_2$, -COSH, -COSR-, CSOR, NO_2, $-OSO_3H$, $-SO_3H$, , -SOR, or $-SO_2R$;

X is selected from the group consisting of: OH, -OR, $-O_2CR$, -SH, -SR, -SOCR, $-NH_2$, -NHR, $-NR_2$, $-NR_3^+$, -NHCOR, -I, -Br, -Cl, -F, -CN, $-CO_2H$, $-CO_2R$, -CHO, -COR, $-CONH_2$, -CONHR, NRCOR, $-CONR_2$, -COSH, -COSR-, CSOR, NO_2, $-OSO_3H$, $-SO_3H$, , -SOR, $-SO_2R$, $-SO_2NH_2$, $-SO_2NHR$, and $-SO_2NR_2$; and,

R is a linear, branched, or cyclic one to ten carbon, saturated, partially saturated, or unsaturated alkyl group;

providing that the compound is not pelorol.

2. The compound or salt of claim 1, wherein U_1, U_2, U_3 and U_4 are independently CH, CX, or CR_1.

3. The compound of claim 2, wherein U_1, U_2, U_3 and U_4 are independently selected from CH, COR, and COH.

4. The compound or salt of claim 1, 2, or 3, wherein Z is an alkyl chain of 3, 4, or 5 atoms, being carbon atoms or carbons in C, CH, or CH_2 groups which have been replaced as defined.

5. The compound or salt of any one of claims 1-4, wherein W is an alkyl chain of 2 or 3 atoms, being carbon atoms or carbons in C, CH or CH_2 groups which have been replaced as defined.

6. The compound or salt of any one of claims 1-5, wherein Y is an alkyl chain of between 1 and 3 atoms, being carbon atoms or carbons in C, CH, or CH_2 groups which have been replaced as defined.

7. The compound or salt of any one of claims 1-6, wherein Z has a chain of 4 atoms.

8. The compound or salt of any one of claims 1-7, wherein W has a chain of 2 atoms.

9. The compound or salt of any one of claims 1-8, wherein Y has a chain of 1 or 2 atoms.

10. The compound or salt of any one of claims 1-9, wherein the atoms of the chains of Z, W, and Y are carbon atoms.

11. The compound or salt of claim 1, selected from the group consisting of homopelorol, PNSR-4A, PNSR-5A, PNSR-6A, PNSR-8A and PNSR-9A.

12. A method of treatment or prevention of an immune, inflammatory, or neoplastic condition or disorder, comprising administering to a patient in need thereof, an effective amount of one or more of: pelorol and a compound as defined in any one of claims 1-11, or pharmaceutically acceptable salts thereof.

13. The method of claim 12, wherein the treatment or prevention is of an inflammatory condition associated with rheumatoid arthritis, multiple sclerosis, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease, host versus graft disease, lupus erythematosis, Alzheimer's disease, capillary leak syndrome, insulin-dependent diabetes mellitus, osteoporosis or another disease related to inappropriate activation of macrophage-related cells of the reticuloendothelial lineage.

14. The method of claim 12, wherein the treatment or prevention is of a neoplastic disorder, wherein the disorder is a leukemia, carcinoma, sarcoma, melanoma, neuroblastoma or a hematological malignancy.

15. The method of claim 14, wherein the disorder is a leukemia.

16. The method of claim 12, wherein the treatment or prevention is of an allergy.

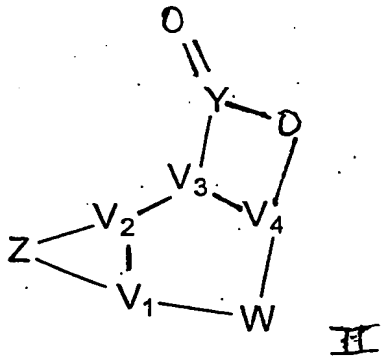
17. A pharmaceutical composition for the treatment or prevention of an immune, inflammatory, or neoplastic condition or disorder comprising a pharmaceutically acceptable carrier and one or more of pelorol and a compound as defined in any one of claims 1-11, or pharmaceutically acceptable salts thereof.

18. The use of pelorol or a compound as defined in any one of claims 1-11 or a salt thereof, for modulation of SHIP 1 activity.

19. The use of pelorol or a compound as defined in any one of claims 1-11 or a salt thereof, for preparation of a medicament for modulation of SHIP 1 activity.

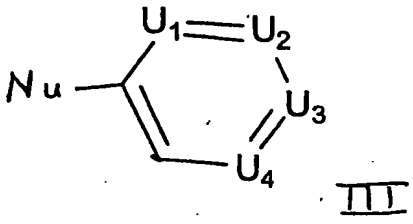
20. The use of claim 18 or 19, wherein the modulation is agonistic.

21. A method of making a compound of Formula I as defined in claim 1, comprising: combining a lactone of Formula II:



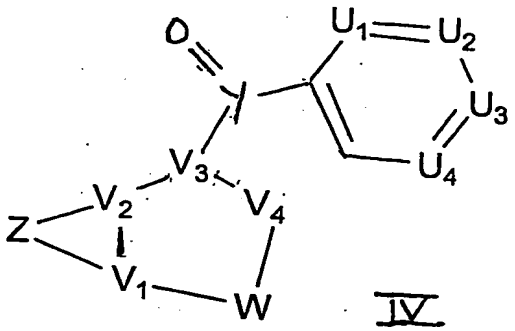
II

in which V_1-V_4, Y, W and Z are as defined for Formula I, with an aromatic ring of Formula III:



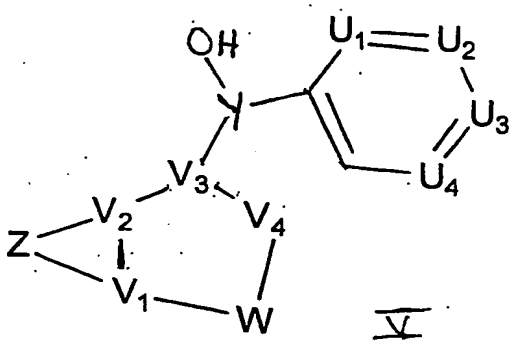
III

in which U_1-U_4 are as defined for Formula I and Nu is a nucleophilic reactive group, to produce a compound of Formula IV:



IV

reducing the compound of Formula IV to produce a compound of Formula V:



V

condensing the compound of Formula V to produce a compound of Formula I.

22. The method of claim 21, wherein the compound of Formula I produced thereby comprises an unsaturated moiety in Y and the method further comprises oxidizing and reducing the compound comprising an unsaturated moiety in Y to reduce the number of atoms in the ring comprising Y.

5

23. The method of claim 21 or 22, wherein the compound of Formula II is sclareolide.

24. The method of any one of claims 21-23, wherein U_2 in the compound of Formula III is an activating group.

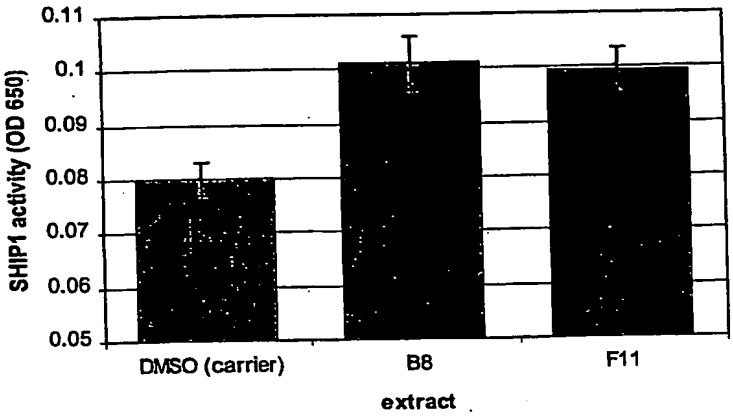


FIGURE 1

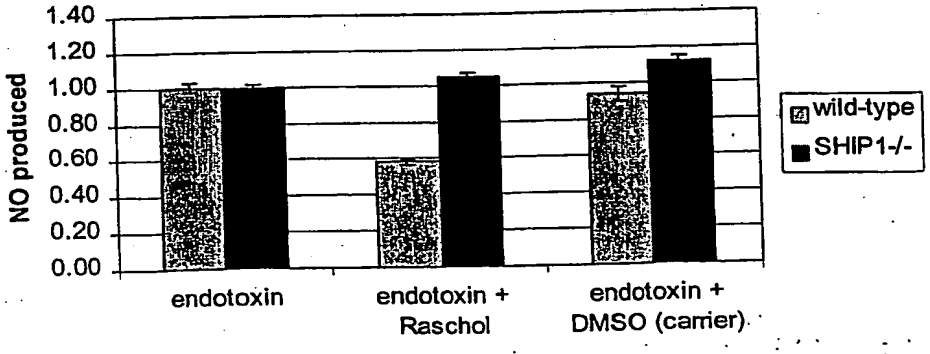


FIGURE 2

PCT/CA 02/01550

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J63/00 A61P35/00 A61P35/02 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HE W ET AL: "Novel cytokine release inhibitors. Part III: truncated analogs of tripterine" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 24, 15 December 1998 (1998-12-15), pages 3659-3664, XP004150387 ISSN: 0960-894X page 3663, table 2, compound 23 --- -/--	1-10,12, 13,16,17

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 2003	28/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Watchorn, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SOROKINA, I. B. ET AL: "Estrogen and antineoplastic activity in a series of transformed estrone and estradiol analogs" retrieved from STN Database accession no. 80:91450 XP002230773 abstract & IZVESTIYA AKADEMII NAUK SSSR, SERIYA BIOLOGICHESKAYA (1973), (5), 664-70 ,	1-10,12, 14,17
X	HARRING SCOTT R ET AL: "Polyene cascade cyclizations mediated by BF-3 cntdot CH-3NO-2. An unusually efficient method for the direct, stereospecific synthesis of polycyclic intermediates via cationic initiation at non-functionalized 3 alkenes. An application to the total synthesis of (racemic)-taxodione." TETRAHEDRON, vol. 50, no. 31, 1994, pages 9229-9254, XP002230772 ISSN: 0040-4020 page 9237; example 14	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 02/01550

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-16,18,20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-10,12-21 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10,12-21 (in part)

Present claim 1-10 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 11. The search was also carried out for the use of compounds of claim 1, where Z is a chain of four carbon atoms, W is a chain of 2 atoms and Y is a chain of 2 atoms and these are all chains of carbon atoms, for the treatment of neoplastic disease and immune disorders.

The search on the methods, compositions, and uses of the compounds of claims 1-11 according to claims 12-20 have been limited in the same way and the process of claims 21-24 has only been searched insofar as it produces the compounds of claim 11.

In addition to the above reasons, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to the subject matter identified above. In this regard it should be noted that the applicant has drafted an extremely broad claim with one particular recognisable technical feature, namely the aromatic steroid D-ring. However, the presence of an aromatic D ring can simply be achieved by inverting by 180 degrees, the structure of a plethora (several thousand) known A-ring aromatic steroid compounds. The applicant has simply drawn these known compounds in a projection which is rotated by 180 degrees relative to the normal IUPAC designated projection for steroid compounds to result in a structure which appears to have an aromatic D-ring, but is in fact identical to a steroid with an aromatic A ring, which are very well known compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.